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## REMARKS

### **Status of the Claims**

From the last set of claim amendments that were entered, claims 1-12 are currently pending. In the present Response, claim 12 is cancelled; claims 1-11 are amended; and new claims 13-28 are added. Thus, after entry of these amendments, claims 1-11 and 13-28 are presented for consideration.

Pursuant to the Office Action, claims 1-11 are rejected under 35 U.S.C. §112, first paragraph. Claims 1-11 are rejected under 35 U.S.C. §112, second paragraph. Applicants respectfully traverse all outstanding objections to the specification and rejections of the claims.

### **Support for the Claim Amendments**

Claims 1-11 have been amended to more particularly describe the invention as well as to clarify the issues raised in the official Actions. Support for new claims 13 and 14 drawn to polynucleotides having at least 70% identity to polynucleotides that encode the polypeptide having the sequence as set forth in SEQ ID NO:28, or enzymatically active fragments thereof, and polynucleotides that encode polypeptides having 70% identity to SEQ ID NO:28 can be found, *inter alia*, page 23, lines 15-19; and page 25, lines 7-11. Support for new claims 15-19 can be found in claims 1, 2, 5, 10, and 11, respectively, as originally filed. Support for new claims 20 and 21 directed to fragments can be found, *inter alia*, at page 21, lines 23-28. Support for the term "hybridizes with specificity" can be found, *inter alia*, at page 37, lines 16-17. Support for hybridization conditions can be found, *inter alia*, at page 37, lines 16-25. Support for new claims 22-27 directed to polynucleotide probes can be found, *inter alia*, at page 18, lines 16-19 (nucleic acid sequences hybridizing to specific nucleic sequences under stringent conditions); page 21, lines 23-31 (probes having at least 10, 15, 30, 50 or 150 bases); page 23, lines 6-25 (polynucleotides having at least 15, 30, or 50 bases which hybridize to any part of a polynucleotide of the present invention); and page 25, lines 7-13 (polypeptides of the invention

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can have at least 90% identity to SEQ ID NO:28). Applicants submit that no new matter has been introduced by the present amendments.

### **Issues under 35 U.S.C. §112, first paragraph**

A review of the present prosecution file indicates that there have been several Responses and Advisory Actions since the final Office Action. Applicants wish to take this opportunity to clarify the issues.

In the most recent Advisory Action, the Patent Office pointed out that the previous amendments of 1/3/2002, Paper No. 19 and 3/14/2002, Paper No. 24, were not entered. Accordingly, Applicants' instant amendments are to claims as they stood in the Response filed 5/23/01. Applicants have attempted to consider and address, where appropriate, all the 35 U.S.C. §112 rejections raised in the 8/14/01 final Office Action, 1/16/02 Advisory Action, 4/9/02 Advisory Action, and 6/19/02 Advisory Action.

Claims 1-11 have been amended to more particularly describe the polynucleotides and polypeptides of the invention. Claims 3, 4, 10 and 11 have been amended to change the dependencies with the addition of new claims. New claims 13 and 14 are drawn to polynucleotides having at least 70% identity to a polynucleotide that encodes for SEQ ID NO:28, or fragments thereof, or polynucleotides encoding a polypeptide having at least 70% identity to SEQ ID NO:28, or fragments thereof, wherein the claimed polynucleotide encodes a polypeptide having phosphatase activity. The new claims further recite polynucleotides that are complementary to the aforementioned polynucleotides. New claims 15-21 were added to separate out the issues concerning claims directed to polynucleotides comprising at least 15 contiguous bases of the claimed polynucleotides and polypeptides comprising at least 30 amino acids of the claimed polypeptides.

It appears from page 3, line 23, to page 4, line 2; and page 4, lines 10- 15, of the final Office Action mailed on August 14, 2001, that the Patent Office acknowledges that the specification adequately describes polynucleotides having 100% to 70% identity to the disclosed polynucleotide and encoding the protein of SEQ ID NO:28 (SEQ ID NO:19 is a nucleic acid

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sequence and SEQ ID NO:28 is the amino acid sequence) are adequately described. The Patent Office further acknowledges that the specification enables enzymatically active proteins having the amino acid sequence at least 70% identical to SEQ ID NO:28 or enzymatically active fragments thereof, as well as polynucleotides which encode these proteins.

However, on pages 3 and 4 of that same Office Action, the Patent Office alleges that polynucleotides, which do not themselves encode a thermostable phosphatase but merely hybridize to a polynucleotide that encodes a thermostable phosphatase, do not themselves have a defined function. The Patent Office alleges that while the limitation that they hybridize to specific polynucleotides may be sufficient for an adequate structural description of the claimed polynucleotides, their functional limitation remains undefined and therefore applicants have not described the structure/function relationship of the claimed polynucleotides. The Patent Office further alleges that polynucleotides that comprise 15 contiguous bases of a polynucleotide or enzymes that comprise at least 30 contiguous amino acids are not considered to be adequately described with respect to structure.

Moreover, the Patent Office alleges that methods to produce variants of a known sequence requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. The Patent Office alleges that this would be undue experimentation. As there were three responses after final filed and three Advisory Actions mailed, it is not altogether clear if the Patent Office was persuaded, in part, by any of the arguments presented in the subsequent responses. Applicants will, therefore, address the issues *de novo*.

### ***Written Description***

The Patent Office alleges that polynucleotides which do not themselves encode a thermostable phosphatase, but merely hybridize to a polynucleotide that encodes a thermostable phosphatase, do not themselves have a defined function. Applicants respectfully disagree. One of the defined functions of polynucleotides of the invention having at least 15 contiguous bases is that they can be used as probes for identifying polynucleotides that encode polypeptides

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having a phosphatase activity (see, *e.g.*, page 23, lines 6-14 of the specification). It would have been well within the knowledge of one skilled in the art, at the time of filing, to design probes based upon the written disclosure of the sequences provided in the specification (the structure). The specification also provides an exemplary function of the polynucleotides, *i.e.*, to identify polynucleotides that encode for a polypeptide having a phosphatase activity (see, *e.g.*, page 36, line 24, to page 37, line 7 of the specification). It is also well known in the art that probes at least 15 nucleotides long can be used to specifically identify or detect polynucleotides. For example, such probes are used routinely to screen libraries for desired polynucleotides.

The Patent Office alleges that while the limitation that they hybridize to specific polynucleotides may be sufficient for an adequate structural description of the claimed polynucleotides, their functional limitation remains undefined and therefore applicants have not described the structure/function relationship of the claimed polynucleotides. Applicants respectfully submit that the Patent Office's statement sets forth the relationship between structure and function of the claimed polynucleotide. The Patent Office has stated that the limitation that they (polynucleotides comprising at least 15 contiguous bases) hybridize to specific polynucleotides may be sufficient for an adequate structural description of the claimed polynucleotides. It appears that the Patent Office is stating that the function (ability to hybridize) can be used to determine structure. In a similar manner, Applicants submit that this structure can determine its function (ability to hybridize to a polynucleotide that encodes a polypeptide having phosphatase activity). In other words, the relationship between structure and function is that the structure of a polynucleotide (*i.e.*, contents of its sequence) affects its function (*i.e.*, ability to hybridize to a particular polynucleotide).

Thus, Applicants respectfully submit that the application provides the structure of the claimed invention by disclosing the sequence of the enzyme SEQ ID NO:28, a method for measuring similarity/identity, which one skilled in the art could use to identify polynucleotides of the invention, and an assay for detecting function, *i.e.*, ability to hybridize to polynucleotides encoding polypeptides having phosphatase activity. Therefore, the specification describes the claimed polynucleotides in terms of structure and function.

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With respect to the written description requirement for a phosphatase having 30 contiguous amino acids of an amino acid sequence which is at least 70% identical to SEQ ID NO:28, Applicants respectfully refer the Patent Office to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. §112, first paragraph. In example 14 of the guidelines (a copy of which is attached for the Examiner's convenience), a claim reciting variants claimed by sequence identity to a sequence is sought. In the example, the specification is described as providing SEQ ID NO:3 and a function for the protein. The specification contemplates, but does not exemplify variants of SEQ ID NO:3 that can have substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions, and additions are routine in the art and provides an assay for detecting the activity of the protein. The analysis of example 14 states that procedures for making variants are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. The conclusion states that the disclosure meets the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention.

Analogously, the instant specification indicates that in the claimed genus of polypeptides that are variants of SEQ ID NO:28, all must have phosphatase activity and all must have at least 70% identity to SEQ ID NO:28. As the guidelines recognize that written description is met for a genus of polypeptides that have 70% identity to SEQ ID NO:28, the polypeptides having 30 contiguous amino acids of the genus of polypeptides must also meet the written description requirements. Therefore, Applicants respectfully submit that the pending claims meet the written description requirement under 35 U.S.C. §112, first paragraph.

### ***Enablement***

The Patent Office alleges that methods to produce variants of a known sequence requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. The Patent Office alleges that this would be undue experimentation. Applicants respectfully disagree. In the present application, Applicants have disclosed the amino acid sequence (*i.e.*, structure) of a novel polypeptide having

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phosphatase activity. It should be mentioned that at the time the instant application was filed, the state of the art and level of skill of the artisan in the field of molecular biology was very advanced. Thus, armed with the disclosure provided in the application, one of ordinary skill in the art can use well-known laboratory techniques to create variant polypeptides having at least 70% identity and also polypeptides having at least 30 contiguous amino acids of the variants. The disclosure provides an assay for testing the polypeptides for phosphatase activity (see page 39 of the specification).

Accordingly, based on Applicants' disclosure, the claimed invention is properly enabled for one skilled in the art to practice the invention. The Patent Office has alleged that this is undue experimentation. Applicants respectfully aver, however, that it would be a matter of routine experimentation, not undue experimentation, for one skilled in the art.

Regarding undue experimentation, the Federal Circuit in *In re Wands* directed that the focus of the enablement inquiry should be whether the experimentation needed to practice the invention is or is not "undue" experimentation. The court set forth specific factors to be considered.

One of these factors is "the quantity of experimentation necessary." Guidance as to how much experimentation may be needed and still not be "undue" is set forth by the Federal Circuit in, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*<sup>1</sup> An applicant had claims that were generic to all IgM antibodies directed to a specific antigen. However, only a single antibody producing cell line had been deposited.<sup>2</sup> The PTO had rejected claims that were generic to all antibodies directed to the antigen as lacking an enabling disclosure.

The Federal Circuit reversed, noting that the evidence indicated that those skilled in the monoclonal antibody art could, using the state of the art and applicants' written disclosure, produce and screen new hybridomas secreting other monoclonal antibodies falling within the genus without undue experimentation. The court held that applicants' claims need not be limited

<sup>1</sup> *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

<sup>2</sup> The cell line was a hybridoma, thus, all of the antibodies it produced had the same structure and activity.

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to the specific, single antibody secreted by the deposited hybridoma cell line (significantly, the genus of antibodies was allowed even though only one antibody species was disclosed). The court was acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation."

Analogously, practitioners of molecular biology for the instant invention also recognize that many constructs may need to be created/isolated and analyzed to isolate the claimed polypeptides and polynucleotides. However, the procedures for isolating polypeptides, creating variant polypeptides, and utilizing sequences such as for the construction of probes are widely accepted, routine protocols, not requiring "undue experimentation" to be practiced. Accordingly, one skilled in the art has sufficient guidance by the specification to practice the claimed methods without undue experimentation.

In light of the amendments and arguments presented herein, Applicants respectfully request reconsideration and withdrawal of the rejection based upon 35 U.S.C. §112, first paragraph.

#### **Actions subsequent to the final Office Action**

In the 1/16/02 Advisory Action mailed in reply to a response filed by the Applicants on 11/14/01, the Patent Office maintains the rejection under 35 U.S.C. §112, first paragraph, lack of enablement and lack of written description. In particular, the Patent Office alleges that the mere limitation that a polynucleotide hybridizes to a polynucleotide that encodes a phosphatase does not necessarily mean that the claimed polynucleotide is useful in an assay as a probe for the identification for nucleotides. Applicants have presented polynucleotides having at least 15 contiguous bases of the claimed polynucleotides in new claims 15, 16, 17, 20, and 21 so that the polynucleotides having at least 15 contiguous bases specifically hybridize to polynucleotides that encode a phosphatase.

The Advisory Action also did not find persuasive the argument that phosphatases comprising as little as 30 amino acids of the claimed polypeptides had a nexus between structure

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and function. Applicants submit that the arguments presented in the written description section set forth above overcome this issue.

In the 4/9/02 Advisory Action mailed in reply to a response filed by the Applicants on 3/14/02, the Patent Office maintains the rejection under 35 U.S.C. §112, first paragraph, lack of enablement and lack of written description. In particular, the reasons for rejection raised in the previous Advisory Action are repeated.

In the most recent 6/19/02 Advisory Action mailed in reply to a response filed by the Applicants on 5/30/02, the Patent Office maintains the rejection under 35 U.S.C. §112, first paragraph. In particular, the rejection raised against the polynucleotide having at least 15 contiguous bases is repeated.

Applicants respectfully submit that these issues raised by the Patent Office have been addressed by the instant response and amendment.

#### **Issues under 35 U.S.C. §112, second paragraph**

Applicants have amended the claims to overcome the rejections raised in the final Office Action and Advisory Actions and request withdrawal of all issues outstanding in the rejection of claims 1-11 based upon 35 U.S.C. §112, second paragraph.

#### **CONCLUSION**

Claims 1-12 are pending in the application. Claim 12 has been cancelled; claims 1-11 have been amended; and claims 13-28 have been added by the present Response. Applicants request that the Examiner reconsider the application and claims in light of the foregoing reasons and amendments and respectfully submit that the claims are in condition for allowance.

If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues and to work with the Examiner toward placing the application in condition for allowance.

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Attached is a marked-up version of the changes being made by the current amendment.

Applicants believe that no fees are necessitated by the present Response. However, in the event any fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 06-1050.

Respectfully submitted,

Date:

July 22, 2002

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**Version with markings to show changes made**

**In the claims:**

Claim 12 has been cancelled.

Claims 1-11 have been amended as follows:

1. (Twice Amended) An isolated polynucleotide selected from the group consisting of:  
(a) a polynucleotide encoding a thermostable phosphatase comprising an amino acid sequence as set forth in SEQ ID NO: 28; and  
(b) a polynucleotide which is complementary to the polynucleotide of (a);[; and  
(c) a polynucleotide comprising at least 15 contiguous bases of the polynucleotide of (a);  
wherein the polynucleotide encodes a polypeptide having activity as a thermostable phosphatase.]
2. (Twice Amended) An isolated polynucleotide selected from the group consisting of:  
(a) SEQ ID NO: 19; and  
(b) SEQ ID NO: 19, where T can also be U;  
wherein the polynucleotide of (a) and (b) encode a phosphatase.[and  
(c) fragments of a) or b) that are at least 15 contiguous bases in length and that will hybridize to DNA which encodes the amino acid sequence of SEQ ID NO: 28; wherein the isolated polynucleotide encodes a thermostable phosphatase, or an enzymatically active fragment thereof.]
3. (Amended) The polynucleotide of [Claim 1] claims 1, 2, 13, or 14, wherein the polynucleotide is DNA.
4. (Amended) The polynucleotide of [Claim 1] claims 1, 2, 13, or 14, wherein the polynucleotide is RNA.

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5. (Twice Amended) An isolated polynucleotide encoding a thermostable phosphatase, or an enzymatically active fragment thereof, comprising a polynucleotide having at least 70% identity to a member selected from the group consisting of:

(a) a polynucleotide encoding an enzyme having phosphatase activity encoded by the DNA contained in ATCC Deposit No. 97379, wherein said enzyme is obtained from *Ammonifex degenesii* KC4; and

(b) a polynucleotide complementary to the polynucleotide of (a).; and

(c) a polynucleotide comprising at least 15 contiguous bases of the polynucleotide of (a); wherein the polynucleotide has thermostable phosphatase activity.]

6. (Amended) A vector comprising the DNA of [Claim 1 or Claim 2] claim 3.

7. (Amended) A host cell comprising the vector of [Claim] claim 6.

8. (Amended) A process for producing a polypeptide comprising: expressing from the host cell of [Claim] claim 7 a polypeptide encoded by said DNA and isolating the polypeptide.

9. (Amended) A process for producing a recombinant cell comprising: transforming or transfecting the cell with the vector of [Claim] claim 6 such that the cell expresses the polypeptide encoded by the DNA contained in the vector.

10. (Twice Amended) A thermostable phosphatase of which at least a portion is encoded by a polynucleotide of claim 14 [1], and wherein [which is selected from the group consisting of

(a) a) the thermostable phosphatase comprises [comprising] an amino acid sequence which is at least 70% identical to an amino acid sequence as set forth in SEQ ID NO: 28[; and

(b) a thermostable phosphatase which comprises at least 30 contiguous amino acid residues of the enzyme of (a)].

11. (Twice Amended) A phosphatase [An] enzyme of which at least a portion is encoded by a polynucleotide of claim 14 [1], and wherein [which is selected from the group consisting of:

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(a) a thermostable] the phosphatase comprises [comprising] an amino acid sequence which is at least 70% identical to the amino acid sequence as [selected from the group of amino acid sequences] set forth in SEQ ID NO: 28[; and

(b) a thermostable phosphatase which comprises at least 30 contiguous amino acid residues of the enzyme of (a)].

Claims 13-28 have been added.

**Example 14: Product by Function**

**Specification:** The specification exemplifies a protein isolated from liver that catalyzes the reaction of  $A \rightarrow B$ . The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

**Claim:**

A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of  $A \rightarrow B$ .

**Analysis:**

A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.

A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3. Additionally, the claim is drawn to a protein which comprises SEQ ID NO: 3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising".

The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.

A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious.

There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that

applicant was in possession of the necessary common attributes possessed by the members of the genus.

**Conclusion:** The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.